Diagnosis and Treatment of Dementia

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Overview

- Epidemiology
- Age associated Cognitive Changes
- Diagnosis
- Differential Diagnosis
- Etiology
- Workup
- Non-pharmacologic Treatments
- Drug Treatments
- Terminal Care
Epidemiology

- Prevalence:
  - 1% at age 60
  - Doubles every five years
  - 30-50% by age 85
  - Prevalence curve flattens out at about age 90
- 4th leading cause of death in the elderly
- Life expectancy after diagnosis 3-15 years, recent data suggests shorter life expectancy

Wolfson, NEJM April, 2001

Epidemiology of Alzheimer’s

- Accounts for 60-70% of dementia in US
- Risk factors:
  - Older age
  - Family history
    - (ε4 allele and other chromosomal defects)
    - 3x risk with 1st degree relative
  - Lower education level
Other Causes of Dementia

- Dementia with Lewy Bodies
  - #2 in autopsy studies, males > females
  - Parkinsonism, little benefit from sinemet, fluctuating impairment, visual hallucinations, neuroleptic sensitivity, rapid progression
- Frontotemporal Dementias: e.g. Pick’s disease
  - Personality changes, euphoria, apathy, disinhibition, compulsive behaviors
  - Relatively preserved visuospatial function

Other Causes of “Cognitive Impairment”

- PSP & related disorders
- Huntington’s
- Post-anoxic
- NPH
- B12
- Hypothyroidism
- Hypercalcemia
- Alcohol/thiamine
- Infections
  - HIV
  - Syphilis
  - Lyme’s
  - CJD
  - Encephalopathy
    - Uremic
    - Hepatic
“Reversible Dementias”

- More properly called “potentially reversible cognitive impairments”
- Candidates: Drug induced, depression, thyroid, B12, NPH, subdural hematoma
- Truly reversible <1-3%
- Most patients go on to develop dementia


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Diagnosis of Dementia

- Multiple cognitive deficits manifested by impaired memory plus:
  - Impaired language or
  - Apraxia or
  - Agnosia or
  - Impaired executive function
- Deficits:
  - Significant enough to impair function
  - Interferes with work or social activities
- Not delirium
Differential Diagnosis

- Delirium
- Depression
- Psychotic disorders
- Medication induced cognitive problems
- Sensory deficits
- Aphasia
- Developmental disability
- Low literacy or education

Age Related Cognitive Changes

- More trouble with difficult tasks when distracted
- Slower information processing
- Some decline in process oriented manipulative aspects of short term memory
- Primary problem in long term memory is recall, not recognition
- Most common complaint: word (name) finding
The Workup

- History: onset, personality, meds, family, social supports, functioning
  - Labs: CBC, lytes, Ca, Cr, Bun, Glu, TSH, B12
  - Consider: HIV, RPR, LFTs, heavy metal screen, rarely LP
- Neuroimaging: Highest yield in young, rapid onset, seizures, gait abnormality, focal exam  
  Patterson 1999

When is Neuropsychological Testing Helpful?

- Complex differential, such as distinguishing depression from dementia
- To diagnose highly or marginally functional adults (“floor” or “ceiling” effects)
- Very mild impairments
- May help in competency determination
- May help with management and family recommendations
Alzheimer’s disease

- November 3, 2006: 100th anniversary of 37th meeting of German Psychiatrists in Tubingen, Germany
- Alois Alzheimer described a patient with memory decline and other cognitive domains, neuropathological findings of senile plaques and neurofibrillary tangles

Alzheimer’s Disease

- Now known to be the most common cause of dementia
- The number of Americans has doubled with the disease since 1980; now about 4.5 million
- Number affected may triple again by 2050.
- Intense burden on families, as 70% of patients are cared for at home
AD: Etiology

- Presence of amyloid plaques, neurofibrillary tangles characteristic features at autopsy
- Symptoms thought to be due to decrease in cholinergic innervation of the cerebral cortex and basal forebrain
- This theory led to the development of drugs designed to increase the activity of cholinergic systems in the CNS

Alzheimer’s Disease

- Degenerative brain disease that targets the basal forebrain and medial temporal lobe structures (cholinergic)
- This includes the hippocampus, amygdala, and entorhinal cortex
- Memory loss occurs as an early symptom
Alzheimer’s Disease: COSTS

- The cost of care for AD patients is about $42,000 annually, $174,000 over the patient’s lifetime.
- These figures do not account for potentially reversible conditions that are mistaken for AD, lost productivity from few patients with early AD, or caregiver stress.

Alzheimer’s Disease’s Disease

- Characteristic “cortical” clinical features:
  - Aphasia
  - Apraxia
  - Agnosia: The inability to recognize and identify objects or persons despite having knowledge of the characteristics of those objects or persons
  - Then, consequent amnesia and personality changes
Alzheimer’s disease variants

- Posterior cortical atrophy
- Progressive or fluent aphasia
- Progressive apraxia
- FTD
- The more posterior forms can be less likely to present with behavioral problems.

NINCDS criteria for probable, possible, and definite AD

- Probable AD: Dementia established by clinical criteria
- Dementia confirmed by cognitive testing
- Deficits in 2 or more domains of cognitive testing
- Progressive decline of memory and other cognitive features
- Onset between ages 40 and 90 years
Possible AD criteria

- Atypical onset, presentation, or clinical course of dementia
- Another illness is capable of producing dementia, but is not considered to be the primary cause
- DEFINITE AD: clinical criteria for probable AD
- Tissue diagnosis by autopsy or biopsy

DSM-IV criteria for AD

- Insidious onset with progressive decline of cognitive function, with impairment of social or occupational functioning from previous higher level
- Impairment of recent memory
- Disturbance of at least one of the following: aphasia, apraxia, agnosia, executive functioning (planning, organizing, abstracting, sequencing)
Nonpharmacologic Treatment

- Evaluation of Patient
  - MMSE or other cognitive tool helpful to follow
  - Functional assessment every 6-12 months
  - Behavioral interview with each visit (sleep, wandering, eating, hallucinations, agitation)

Caregiver Evaluation

- Alzheimer Association Referral
- Depression, coping, abuse potential, need for placement or community resources
Support and Education

- Randomized controlled intervention study of 206 spouse caregivers of AD patients followed over 3 & 1/2 years
- Intervention: 6 sessions of individual counseling, follow-up support groups, and availability of counselor to help
- Time to NH placement was 329 days longer in the treatment group

Mittelman JAMA 1996

Brain Imaging

- Assess for relevant structural pathology (tumors, vascular lesions, subdural hematomas, hydrocephalus)
- Look for atrophy in the medial temporal lobe
- Cerebral white matter hyperintensities common in AD
Laboratory Investigation

- No commercially available biomarker for AD currently
- Diagnosis is made by clinical recognition, exclusion of other factors
- Thyroid function, vitamin B12, complete blood counts, LFT’s, Renal function, Calcium
- ESR, chest x-ray is there is history of lung cancer, baseline EKG

CSF (Lumbar Puncture)

- Rapid progression, myoclonus, depressed level of consciousness
- Lumbar puncture may be necessary
- Rule out infection, malignancy, inflammatory disease
Biomarkers for AD

- Controversial
- CSF measurement of amyloid beta-peptide and tau proteins
- AD patients have CSF reductions in Abeta 42 and increases in tau
- There is overlap between AD and some other groups

Neuropathology

- Definitive diagnosis: requires microscopic examination of cerebral cortex
- Cortical senile plaques
- Neurofibrillary tangles
- Ultimately, the loss of synapses and neurons
AD: Plaques

- Plaques are formed from deposition of amyloid beta-peptide that deposits in the form of amyloid
- “Amyloid hypothesis” states that the Abeta aggregation is the primary event leading to AD
- All other changes including neurofibrillary tangles are secondary

Genetics

- Early onset familial AD: autosomal dominant mutations found on genes for the amyloid precursor protein (APP) on chromosome 21, presenilin 1 on chromosome 14, and presenilin 2 on chromosome 1
Genetics

- The genetic risk factor that accounts for more cases of AD than any other is apolipoprotein E (APOE) e4 allele on chromosome 19
- Associated with late-onset familial and “sporadic” AD
- APOE e4 is a prevalent risk factor for AD.

Donepezil (Aricept)

- Is a novel, piperidine derivative
- Lack of peripheral activity
- While it significantly inhibits brain cholinesterase, has no effect on heart or smooth muscle in the intestine
- Long plasma half-life (70 hours)
- Renal excretion and cytochrome P450
Donepezil (Aricept)

- While the drug is currently indicated for mild to moderate Alzheimer’s, there is also evidence from 2 trials that it may be effective for moderate to severe disease
- Donepezil is generally well tolerated
- Common side effects include, nausea, anorexia, abdominal pain, vivid dreams.

Galantamine (Razadyne, Reminyl)

- Reversible, competitive cholinesterase inhibitor and also modulates nicotinic acetylcholine receptors
- Shown to be effective in treatment moderate AD
Galantamine ER (Razadyne)

- 8 mg (white opaque capsule)
- 16 mg (pink opaque capsule)
- 24 mg (caramel opaque capsule)

Galantamine

- Ten high-quality studies (from 12 publications) evaluated galantamine compared with placebo.
- All studies classified individuals as having mild to moderate dementia with a final treatment dose of either 24 mg/d or 32 to 36 mg/d.
Galantamine

- For general cognitive function, pooled evidence showed a statistically significant benefit of galantamine on the ADAS-cog.
- One trial showed a dose-related effect with statistically significant improvement in ADAS-cog score at 24 mg but not at 32 mg.

Rivastigmine (Exelon)

- Rivastigmine (sold under the trade name Exelon) is a parasympathomimetic or cholinergic agent that was developed for the treatment of mild to moderate dementia of the Alzheimer's type.
- In 2006, it became the first product approved globally for the treatment of mild to moderate dementia associated with Parkinson's Disease.
- Available in patch form.
Rivastigmine (Exelon)

- Rivastigmine is a cholinesterase inhibitor that inhibits both butyrylcholinesterase and acetylcholinesterase (unlike donepezil which is selective for acetylcholinesterase).
- It is thought that rivastigmine works by inhibiting these cholinesterase enzymes, which would otherwise break down the brain chemical acetylcholine.

Memantine (Namenda)

- A dysfunction of glutamatergic neurotransmission, manifested as neuronal excitotoxicity, is hypothesized to be involved in the etiology of Alzheimer's disease.
- Targeting the glutamatergic system, specifically NMDA receptors, offers a novel approach to treatment of AD.
Memantine (Namenda)

- Memantine is a low-affinity voltage-dependent uncompetitive antagonist at glutamatergic NMDA receptors.

- Memantine has a much more complex pharmacological profile than originally described. It does in fact work rather similar to the originally introduced drugs that affect acetylcholine-related signaling, in addition to weak actions on glutamate, and has negative effects on neuronal communication at high concentrations.

- A pharmacological analysis showed that this was not due to its ability to block glutamate signaling, but rather to an additional and more potent action on the acetylcholine system.
Donepezil versus Rivastigmine

- One large trial compared donepezil (up to 10 mg/d for 2 years) with rivastigmine (up to 12 mg/d for 2 years) and focused on patients with moderately severe Alzheimer disease for more than 2 years. The results statistically significantly differed in global function (Global Deterioration Scale) and function (Alzheimer disease Co-operative Study–Activities of Daily Living Scale), favoring rivastigmine.

Is statin therapy associated with reduced neuropathologic changes of AD?

- Ginkgo – Mixed results in RCTs
- Is lipoic acid as an anti-inflammatory and neuroprotective treatment for Alzheimer's disease?
- Melatonin?
New Directions in AD

- Vaccines
- Medications that decrease production or increase clearance of amyloid-beta peptides in cells

Diabetes Drugs May Help Alzheimer's

- Researchers have long known that people with diabetes have a higher risk of developing Alzheimer's disease than other people.
Diabetes and Alzheimer’s Disease

- People with diabetes in midlife had up to three times the risk of developing dementia 35 years later.
- Team analyzed samples of brain tissue from 248 patients, stored in the Mt. Sinai Brain Bank.
- Beeri matched 124 patients with diabetes with 124 non-diabetic patients, who were similar to the first group in age, sex and stage of dementia at death.

Diabetes and Alzheimer’s Disease

- Compared with patients who never developed diabetes, patients who had the disease but took insulin along with one additional medication to control blood sugar (typically metformin or glyburide) had 80% fewer brain-clogging amyloid plaques in their brain.
Diabetes and Alzheimer’s Disease

- One theory is that the drugs normalize the communication network of insulin receptors, which go awry in the Alzheimer's brain, somehow restoring those pathways to as close to normal as possible, while clearing out the damaging plaques that form when the network malfunctions.

Behavioral Problems

- Identify and characterize problem behavior: have caregiver keep behavior log
- Consider: delirium, depression, pain, sensory impairments
- Try ABC approach
  - **Antecedent**: What brings it on?
  - **Behavior**: Why is it a problem? For self? Safety? Others? Social norms?
Behavioral Approaches

- Break down activities that may be overwhelming into simple tasks
- Use structured activities and routines to combat boredom and provide external structure
- Change environment rather than patient (e.g. disable stove, make all clothes pull-on sweats in matching colors)
- Quiet voice, simple words and sentences
- Music
- Touch

Drug Treatment of Behaviors

- Identify target symptom (hallucinations, anxiety)
- Anti-cholinesterase drugs may help behaviors and probably have best SE profile
- Neuroleptics help agitation in RCTs (NNT = 5)
- Medication trials largely empiric: donepezil, trazadone, valproate and mood stabilizers, buspirone, SSRIs, benzodiazepines
Behavioral Problems

☐ Identify and characterize problem behavior:
   have caregiver keep behavior log
☐ Consider: delirium, depression, pain, sensory impairments
☐ Try ABC approach
  ■ **Antecedent**: What brings it on?
  ■ **Behavior**: Why is it a problem? For self? Safety? Others? Social norms?
  ■ **Consequences**: Positive (attention) or negative

APA Practice Guidelines

☐ It is generally necessary to see patients in routine follow-up at least every 3–6 months
☐ More frequent visits (e.g., up to once or twice a week) or even psychiatric hospitalization may be required for patients with acute, complex, or potentially dangerous symptoms or for the administration of specific therapies.
APA Practice Guidelines

☐ Recommended assessments include evaluation of suicidality, dangerousness to self and others, and the potential for aggression, as well as evaluation of living conditions, safety of the environment, adequacy of supervision, and evidence of neglect or abuse.

☐ All patients and families should be informed that even mild dementia increases the risk of vehicular accidents.

☐ Mildly impaired patients should be advised to limit their driving to safer situations or to stop driving, and moderately impaired patients should be instructed not to drive.
APA Practice Guidelines

☐ Advice about driving cessation should also be communicated to family members, as the implementation of the recommendation often falls on them.

☐ Three cholinesterase inhibitors—donepezil, rivastigmine, and galantamine—are approved by the U.S. Food and Drug Administration (FDA) for treatment of mild to moderate Alzheimer's disease, and donepezil has been approved by the FDA for severe Alzheimer's disease.

☐ These medications have similar rates of adverse effects and have been shown to lead to modest benefits in a substantial minority of patients (i.e., 30%–40% in clinical trials).
APA Guidelines

☐ These medications should be offered to patients with mild to moderate disease after a thorough discussion of their potential risks and benefits, and they may be helpful for patients with severe Alzheimer's disease.

APA Practice Guidelines

☐ Cholinesterase inhibitors should be considered for patients with mild to moderate dementia associated with Parkinson's disease
☐ Only rivastigmine has been approved by the FDA for this indication, but there is no reason to believe the benefit is specific to this cholinesterase inhibitor.
APA Guidelines

- Cholinesterase inhibitors can be considered for patients with dementia with Lewy bodies.
- Memantine, a noncompetitive N-methyl-D-aspartate (NMDA) antagonist, which has been approved by the FDA for use in patients with moderate and severe Alzheimer's disease, may provide modest benefits and has few adverse effects; thus, it may be considered for such patients.

APA Guidelines

- There is some evidence of its benefit in mild Alzheimer's disease and very limited evidence of its benefit in vascular dementia.
APA Practice Guidelines

- Vitamin E (-tocopherol) is no longer recommended for the treatment of cognitive symptoms of dementia because of limited evidence for its efficacy as well as safety concerns.

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APA Practice Guidelines

- Nonsteroidal anti-inflammatory agents (NSAIDs), statin medications, and estrogen supplementation (with conjugated equine estrogens) have shown a lack of efficacy and safety in placebo-controlled trials in patients with Alzheimer's disease and therefore are not recommended.
APA Practice Guidelines

- On the basis of good evidence, antipsychotic medications are recommended for the treatment of psychosis in patients with dementia and for the treatment of agitation.

APA Guidelines

- Data demonstrating benefit from benzodiazepines are modest, but benzodiazepines occasionally have a role in treating patients with prominent anxiety or on an as-needed basis for patients with infrequent episodes of agitation or for those who require sedation for a procedure such as a tooth extraction or a diagnostic examination.
APA Guidelines

- There is minimal evidence for the efficacy of anticonvulsants, lithium, and beta-blockers for the treatment of psychosis or agitation in dementia, and these medications have significant adverse effects;

- SSRIs may be preferred because they appear to be better tolerated than other antidepressants.

- Agents with substantial anticholinergic effects (e.g., amitriptyline, imipramine) should be avoided.

- Despite the lack of research data, clinical experience suggests that unilateral electroconvulsive therapy (ECT) may be effective for patients who do not respond to pharmacological agents.
APA Guidelines

- Treatments for apathy are not well supported, but psychostimulants, bupropion, bromocriptine, and amantadine may be helpful.

APA Guidelines

- For primarily treating the sleep disturbance, medications with possible effectiveness include trazodone, zolpidem, or zaleplon, but there are few data on the efficacy of specific agents.
- Benzodiazepines are not recommended for other than brief use because of risks of daytime sedation, tolerance, rebound insomnia, worsening cognition, falls, disinhibition, and delirium.
- Diphenhydramine is not recommended because of its anticholinergic properties.
- Antipsychotic medications should not be used solely for the purpose of treating sleep disturbances.
Tube feeding in Dementia

- Background: Malnutrition, weight loss, and poor PO intake is common in late stage dementia
- About one third of feeding tubes are placed in patients with advanced dementia
- Whether to place a feeding tube is a common clinical and ethical dilemma faced by physicians and caregivers of demented patients

Shift away from Tube Feeding

No evidence of prolongation of life, decrease in aspiration, improvement in functional status, decrease in infections, or increase in comfort

Tubes may increase discomfort, result in complications (including death), decrease enjoyment of food, result in restraint use

Restraint use was 77% in one study in demented patients who were receiving tube feeding

Finucane JAMA 1999, Gillick, NEJM 2000
Resources

☐ Alzheimer’s Association: 1-800-660-1993
www.alz.org

☐ Caregiver Resource Centers 1-800-445-8106 www.caregiver.org

☐ Abuse: Local adult protective services or CA State Ombudsman at 1-800-231-4024

☐ ADEAR: www.Alzheimer's.org/adear

☐ Check out Dementia Clinical Practice Guidelines on SF VA Home Page:
  ■ Evaluation, treatment, driving

FTD

☐ Historically, called “Pick’s disease”, Arnold Plck, Prague, 1892

☐ Microscopic abnormalities reported by Alois Alzheimer in 1911; he and Altman described argyrophilic inclusions (Pick bodies) and swollen cells (Pick cells) in frontal and temporal lobes.
Frontotemporal dementia (FTD)

- Focal clinical Syndrome
- Profound changes in personality and social conduct
- Degeneration of the prefrontal and anterior temporal cortex
- Middle age onset
- Survival: about 8 years
- In some familial cases, mutations in the TAU genes
- ?Links to other Tauopathies→PSP, CBD

FTD

- Behavioral changes are usually the presenting feature
- Dominate the clinical course
- Changes in language, cognitive impairment, executive function
- Atrophy of frontal and anterior temporal lobes
- Can occur with motor neuron disease, called “FTD-MND”
FTD Characteristics

- M = F for gender distribution
- Age of onset 45-65 (decade earlier than AD)
- Duration of illness 6 to 8 years
- Family history is common and present in 40% to 50% of patients
- Behavioural change
- Executive dysfunction, changes in speech and language

FTD

- Swearing at inappropriate times
- Outbursts of frustration
- Grabbing food of someone’s plate
- Trying to get out of a moving car
- Re-reading the same book
- Re-visiting the same location
- Overeating
FTM Investigations

☐ Neuropsychology evaluation
☐ Significant impairment on frontal lobe tests
☐ EEG: normal
☐ Brain imaging by MRI: shows predominant frontal or anterior temporal abnormalities

FTD: Treatment?

☐ May have serotonergic abnormalities
☐ SSRI’s: trials have been equivocal
☐ Behavioral problems: antidepressants, neuroleptics
☐ Support network
Differential diagnosis

- FTD
- Frontotemporal lobar degeneration
- Primary progressive aphasia
- Semantic dementia

Vascular dementia

- The second most common form of dementia, after AD
- Loss of executive function, milder memory loss compared with AD
- Associated with cerebral infarction
- Studies show that patients with silent brain infarcts have increased risk of vascular dementia
Vascular dementia

- Criteria for probable dementia: temporal relationship between onset of dementia and occurrence of a stroke
- Arbitrarily determined to be 3 month period of time
- Stepwise decline in cognitive function
- See more sudden onset of dementia

Vascular Dementia

- Different forms of vascular dementia:
  - Due to multiple infarcts
  - Due to posthemorrhagic dementia
  - Due to focal infarcts, such as infarct of frontal lobe
  - Due to subcortical dementia from white matter disease
  - Global hypoxic injury causes cognitive impairment, may be considered a form of vascular dementia
Vascular Dementia

- The most common form is multi-infarct dementia
- May not result in focal neurological deficits
- Over time, cumulative damage results in diminished cognition
- Small strokes are not additive, but cumulative

Vascular dementia

- Step-wise progression, focal symptoms, behavioral abnormalities such as mood disorders earlier than in AD
- AD more associated with global memory impairment, vascular dementia has milder memory impairment
- Binswanger’s disease; result of diffuse ischemic injury to the deep hemispheric white matter
Binswanger’s disease

- Binswanger’s disease presumed to result from thickening and narrowing described as lipohyalanosis with atherosclerotic vascular injury
- Patients have psychomotor retardation, memory deficits, changes in speech, personality changes, urinary dysfunction, and gait unsteadiness

- There may be enlargement of ventricles, but this is due to ex vacuo, due to loss of brain tissue with diffuse cortical atrophy
Vascular dementia

- Annual incidence is 20-40 per 100,000 between persons 60 and 69 years old to 200-700 per 100,000 in persons over 80 years old.
- Prevalence rates double every 5 years.
- Risk is higher in men
- Comprises 10% to 20% of all dementias
- May be higher in Asian and Eastern European countries
- Prevalence is one million in US
- Decreased survival due to cardiovascular disease risk factors

- Risk factors: age, hypertension, diabetes, obesity, cigarette smoking, hyperlipidemia, cardiac disease (CAD, cardiac arrhythmias)
Vascular dementia

- Pathogenesis: Volume loss between 50 and 100 ml produce dementia
- However, even a loss of approximately 20 ml is more frequent in demented subjects than in controls.
- Marked differences between demented subjects and controls are present at the 50 ml cutoff.

- Location of vascular lesions probably more important than volume of tissue destruction
- Angular gyrus, bialteral of left ACA and PCA territories, dominant caudate nucleus, anterior internal capsule interrupting cortico-thalamic and thalamo-cortical pathways, hoppocampus, amygdala, fronto-cingulate gyrus, and basal forebrain.
Vascular dementia

- Cholinesterase inhibitors and memantine produce small benefits in cognition of uncertain clinical significance in patients with mild to moderate vascular dementia.

Diffuse Lewy Body Disease

- Patients with dementia, parkinsonism, visual hallucinations, and rapid eye movement sleep behavior disorder
- Lewy bodies: intracytoplasmic inclusions composed of alpha-synuclein, defining feature of PD
- In PD, Lewy bodies are concentrated in the brain stem substantia nigra
Dementia with Lewy Bodies

- In dementia with Lewy bodies, the structures are present in the substantia nigra, but also in the amygdala, entorhinal cortex, and neocortex.
- Impaired learning, psychomotor slowing, and more visuo-spatial impairment than AD patients.
- However, ¾’s of patients also have neuropathological features of AD.

Summary

- Dementia is very common.
- Primary care physicians need to know how to manage and treat patients with dementia and their caregivers throughout the course of illness.
- Support must be directed at caregiver as well as patient.
- Terminal care is one component of primary care in dementia.